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AND ABSTRACT OF THE LITERATURE

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Changes in the Blood as Reflecting Industrial Damage

Metal Fume Fever: V. Results of the Inhalation by Animals of Zinc and Magnesium Oxide Fumes

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THE JOURNAL OF INDUSTRIAL HYGIENE

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CHANGES IN THE BLOOD AS REFLECTING INDUSTRIAL DAMAGE*

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(From the laboratory of the clinic of Professor Schlossmann in the Medical Academy in Düsseldorf; employing research material provided by Dr. Teleky, Medical Inspector of Factories, Düsseldorf)

IT is of great importance for successful industrial hygiene in the chemical industry to concentrate on the damage to the blood and the blood forming tissues which accompanies the absorption of blood poisons. The blood not only is the most sensitive indicator of internal processes, it not only takes a part and often a predominant part in the industrial damage experienced, but especially early—before the appearance of other readily appreciated changes—one may become aware of generalized damage through recognition of variations in the cellular composition of the blood. And this valuable evidence may be quite characteristic.

In addition to the widely known blood changes in lead poisoning—polychromatophilia and basophilic stippling of the erythrocytes—there are other alterations which are observed in industrial medicine and which are diagnostically and perhaps also prognostically important. This is especially true in regard to the blood picture in benzol poisoning. The American Committee on Benzol (1) has made an exhaustive study of the blood changes in chronic benzol poisoning. A diminution—sometimes after an initial increase—in the leukocyte count was established as a noteworthy and constant early symptom. The differential blood picture showed a relative lymphocytosis of 36 to 49 per cent. as against the normal of 21 to 25 per cent., with a corresponding reduction in the polymorphonuclear neutrophil cells. A reduction in the

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erythrocyte count occurred seldom and was relatively less noticeable. The American authors attributed great significance to these blood changes and advised periodic blood examinations of all benzol workers. They recommended that men should be excluded from work with benzol if they showed a leukocyte count below 5,000 per cubic millimeter, a reduction of more than 25 per cent. in the leukocytes or the erythrocytes, the onset of hemorrhages, or, finally, a fall in hemoglobin below 70 per cent.

Teleky and Weiner (2) also designated lymphocytosis as the characteristic blood finding in benzol poisoning. In slight poisoning they were able to establish relative lymphocytosis as the primary symptom in workers lacking other indications of poisoning. On the basis of this symptom they required cessation of work in benzol prior to the onset of severe symptoms and pronounced changes in the blood, because the action of the benzol can persist in spite of leaving work and can lead to complete degeneration of the blood forming tissues. In addition to lymphocytosis, Teleky and Weiner noticed as an early symptom a slight lowering of hemoglobin, red cells, white cells, and platelets, and in single cases anisocytosis, poikilocytosis, polychromatophilia, and the presence of nucleated red cells. Calamita (3) mentions eosinophilia as a typical finding in benzol poisoning but Teleky and Weiner could not confirm this.

The blood examinations of workmen were amplified by the American investigators through extensive experimental studies on animals, in order to determine the toxicity of benzol and its homologues, xylol, toluol, and a mixture called Hiflash naphtha (4). Subcutaneous injection of these substances into white rats produced a condition resembling chronic industrial poisoning; inhalation and intraperitoneal injection brought on acute intoxication. Xylol and toluol proved less poisonous and in large doses had more of a narcotic action than was found in the case of benzol, which was more poisonous and gave decided central stimulation. Differential leukocyte counts were not made. The disease pictures in acute poisoning through inhalation are given in Table 1.

As a result of daily subcutaneous injections of benzol a specific damage to all the blood forming organs was produced, with a pronounced reduction in the leukocyte count (averaging 91 per cent.). In contrast, toluol produced only slight damage and the blood showed only transient changes: slight reduction in the erythrocyte count, and in five of ten cases an early, transient reduction in the leukocytes of 16 to 37 per cent. At autopsy, in the toluol animals, there was a definite hyperplasia of the lymphatic and myelocytic elements in the bone marrow, of the germinal centers in the lymph glands, and of the malpighian corpuscles in the spleen. Xylol acted, in general, similarly but with less pronounced organic changes and without reducing the leukocyte count.

More dangerous for the blood and blood forming tissues than benzol and its homologues are the nitrated compounds, nitrobenzol, amidobenzol, nitrotoluol, amidotoluol, etc. They

induce methemoglobin formation and its results, cyanosis, dyspnea, toxic jaundice and, as sequelae, aplastic and pernicious anemia. There is little on the blood findings in the German literature. In a case described by Koelsch (5) there was anisocytosis and polychromatophilia of the erythrocytes. The differential blood count showed 67 per cent. polymorphonuclear leukocytes, 3 per cent. eosinophils, 5 per cent. monocytes, and 25 per cent. lymphocytes—normal relative counts. In some other cases only absolute leukocyte and erythrocyte counts are given. More detailed communications are found in the English and the American literature (6) (7) (8) (9), especially with regard to the blood changes in trinitrotoluol workers. In acute poisoning the red as well as the white cell system is damaged. In slight intoxication, through stimulation of the bone marrow, there is an increase in all the cells of marrow origin—erythrocytes, leukocytes, and thrombocytes. Severe poisoning injures the bone marrow and produces a reduction in marrow formed elements. The red cells display signs both of regeneration and of degeneration, polychromatophilia, biliary pigment in their protoplasm, reticulation, stippling, Howell-Jolly bodies, and nucleation. Macrocytes and fragmented cells about one-half normal size are found; these fragmented cells show an irregularly distributed but usually peripheral, intensely staining material (9). Equally characteristic is the white cell picture. It shows lymphocytosis and leukopenia. (See Table 2.) In severe poisoning the bone marrow destruction can be complete, with a resulting aplastic anemia. Panton (7) contributes the following blood findings

TABLE 1.—EFFECT OF INHALATION OF VARIOUS SOLVENTS ON WHITE RATS

SOLVENT	CHANGE IN WT.	REDUCTION IN WHITE CELLS	SYMPTOMS
High Concentration[1]			
	%	%	
Benzol	−28	63	Marked, neurotoxic
Toluol	−21	0	Narcosis, death
Xylol	−10	9	Narcosis, death
Hiflash naphtha	....	...	.....
Moderate Concentration[2]			
Benzol	−14	81	Moderate
Toluol	−3	13	Slight
Xylol	−3	8	Slight
Hiflash naphtha	−10	12	Slight
Low Concentration[3]			
Benzol	−15	91	Prac. none
Toluol	+1	15	None
Xylol	+3	4	None
Hiflash naphtha	−2	9	None

[1] Benzol 2,440 p.p.m. Toluol 1,600 p.p.m. Xylol 1,600 p.p.m.

[2] Benzol 815 to 1,035 p.p.m. Toluol 1,100 and 1,250 p.p.m. Xylol 980 p.p.m. Hiflash naphtha 567 p.p.m.

[3] Benzol 460 p.p.m. Toluol 620 p.p.m. Xylol 620 p.p.m. Hiflash naphtha 312 p.p.m.

TABLE 2.—BLOOD EXAMINATION OF TRINITROTOLUENE WORKERS[1]

DURATION OF WORK IN DAYS	SUMMARY OF SYMPTOMS	WHITE COUNT IN THOUSANDS	PERCENTAGE OF					ABNORMALITIES OF		RED COUNT IN MILLIONS
			Polynuclear Neutrophils	Lymphocytes	Large Mononuclears	Polynuclear Eosinophils	Polynuclear Basophils	Polynuclear Neutrophils	Large Mononuclears	
9	For four days some breathlessness and headache. Two days dizzy with slight tightness in chest and morning nausea. Very slight cyanosis.	11.3	73	17	9	1	0	+	0	4.7
60	For past three weeks rash on body. Had slight tightness in chest and headache and abdominal discomfort.	6.2	48	42	7	3	0	N	N	4.0
28	No symptoms except for bitter taste.	8.0	65	29	5	1	0	N	N	4.5
42	Slight dyspnea for last two days.	13.0	51	37	3	8	1	N	N	4.8
60	Rash on forearms for two weeks. Marked bitter taste; slight abdominal discomfort. Lips somewhat blue.	6.4	62	25	7	5	1	0	sl+	4.0
480	Off and on has had nausea, dizziness, headache, fatigue and tightness in chest; never marked. Slight cyanosis and pallor.	14.4	60	38	2	0	0	N	N	4.3
120	Occasional morning nausea for two weeks, and slight dyspnea. Is slightly cyanotic.	13.5	59	31	4	6	0	sl+	N	4.0
21	Symptoms began four days ago. Considerable fatigue, definite dyspnea, sleeplessness, nausea; occasional cramps in legs. Definite cyanosis.	9.0	55	38	4	3	0	N	N	4.5
35	Shortness of breath since at work. Looks pale and distinctly blue. Slight gastric symptoms.	8.8	67	25	7	1	0	N	N	3.9
21	Marked cyanosis with its usual attending symptoms, dyspnea, etc. Sclerotics slightly yellow.	16.0	64	20	14	1	1	+	++	3.8
30	Slight headache, considerable cough. Some dyspnea. Some gastric symptoms. Weak knees. Dizziness. Slaty color. Liver felt slightly tender.	11.0	49	45	4.5	...	0.5	sl+	sl+	3.7
60	Quite cyanotic and dyspneic, with abdominal symptoms rather marked.	7.0	70	22	7	1	0	N	N	4.2

[1] After Minot (9).

in a fatal case two months before death:

Hemoglobin	35%
Erythrocytes	1,637,000
Color index	1.1
Leukocytes	1,400
Polynuclear neutrophils	20%
Small lymphocytes	50.5%
Large lymphocytes	26.5%
Monocytes	3%

No normoblasts; no morphologic changes in the erythrocytes.

Another case, which was nonfatal, had the following blood picture:

	Oct. 1, 1916	Dec. 7, 1916
Hemoglobin	25%	40%
Erythrocytes	1,410,000	2,225,000
Color index	0.9	0.9
Leukocytes	5,200	16,000
Neutrophils	22%	51.5%
Small lymphocytes	74%	11.5%
Large lymphocytes	..	14.5%
Monocytes	4%	22.5%
Myeloblasts	..	5%
Normoblasts	1%	..

We have had opportunity to make blood examinations on workers in different industrial operations and can now contribute our results.

Benzol, Toluol, and Xylol

In a dye factory where benzol, toluol, and xylol were used, the workers in the solvent room were exposed to fumes in the air as could be recognized by smell. The workers inhaled benzol, toluol, or xylol continuously. In the beginning only pure benzol was used, then xylol, toluol, and 2 to 3 per cent. benzol, and finally xylol, toluol, and benzol in a 5:4:1 relationship. The men had worked for a number of years in these surroundings without noticing any effect on their health. Only in the beginning, when pure benzol was used, were there several complaints of headache and dizziness; one man, slightly poisoned, complained of buzzing in the ears, headache, nausea, and spots before his eyes. In the period 1923 to 1927 these workmen were examined three times. The general examination gave nothing beyond a recognizable pallor. The results of the blood examinations are given in Table 3.

As the table shows, the red cells are not changed. The hemoglobin is normal—rather above normal for inhabitants of the plains. The erythrocytes were, with two exceptions, unchanged with regard to number, shape, and staining. Anisocytosis, poikilocytosis, polychromatophilia, and nucleated red cells were absent. In only a few cases could great differences in cell size be established, more macrocytes than normal being present. The pallor of the workmen was not due to anemia, but apparently had an angiospastic origin. Of the two exceptions, one was a man with lowered red cell count (No. 4), and the other a man with abnormally high erythrocyte and leukocyte counts (No. 15). In neither bodily nor blood condition could anything of etiologic consequence be found in these cases. The diminution in the red count in worker No. 4 was trivial; and if a polycythemia actually existed in the worker Bo (No. 15) it had no significance—rather may one think of a transient concentration of the blood.

The pathognomonic change in the white cell differential blood picture

TABLE 3.—BLOOD FINDINGS FOLLOWING ABSORPTION OF BENZOL, TOLUOL, AND XYLOL

NUMBER	NAME OF WORKMAN	AGE	SUBSTANCE INHALED	DURATION OF WORK		DATE OF BLOOD EXAMINATION	ERYTHROCYTES	HEMOGLOBIN	LEUKOCYTES	DIFFERENTIAL LEUKOCYTE COUNT							
										Polynuclear Neutrophils	Staff-like Neutrophils[1]	Eosinophils	Basophils	Small Lymphocytes	Large Lymphocytes	Monocytes	Plasma Cells
		yrs.		*yrs.*			*per c.mm.*	%	*per c.mm.*	%	%	%	%	%	%	%	%
1	Be.	24	pure benzol	3		July, 1923				45	0	1	0	44	0	10	0
			xylol + toluol			May 25, 1926				49	2	5	0.5	36.5	5	2	0
			+2% benzol	3	7	March 12, 1927				48	1	4.5	0.5	42.5	2.5	1	0
			xylol + toluol														
			+10% benzol	1		April 4, 1927	4,900,000	90	6,400	49.5	3	4	0	33.5	3.5	5.5	1
2	Ro.		pure benzol			July, 1923	.....	...	.....	52	0	4	0	35	0	9	0
3	Ham.		pure benzol			July, 1923	.....	...	.....	65	0	4	0	24	0	7	0
4	Kre.	51	pure benzol	3		July, 1923				63	0	1	0	28	0	8	0
			xylol + toluol		6												
			+2% benzol	3		May 25, 1926	.....	...	.....	37	1	8.5	0.5	44.5	6	2	0.5
5	Ju.		pure benzol			July, 1923	.....	...	.....	54	0	2	0	31	0	13	0
6	Over.		pure benzol			July, 1923	.....	...	.....	52	0	2	0	31	0	15	0
7	Kl.		xylol + toluol	$1\frac{1}{2}$		May 25, 1926				48.5	0	3.5	0	38.5	6	2	1.5
			+2% benzol			March 12, 1927				50	0.5	4.5	1	29.5	7.5	5.5	1.5
			xylol + toluol		$2\frac{1}{2}$												
			+10% benzol	1		April 4, 1927	5,330,000	100	7,200	45.5	2	5	0	39	3.5	4.5	0.5

8	Ho. A.	24	xylol + toluol	½	1½	May 25, 1926				57.5	0.5	3.5	0	31.5	3.5	3	0.5
			+2% benzol			March 12, 1927				48.5	0.5	3.5	1	35	4.5	6.5	0.5
			xylol + toluol			April 4, 1927	5,000,000	95	5,850	38	1.5	5	2	41	4.5	7	1
			+10% benzol	1													
9	Ho. Jos.	29	xylol + toluol			March 12, 1927				41	2	4	2	36.5	7	7.5	0
			+10% benzol	3		April 4, 1927	3,750,000	80	7,500	44.5	3	5	1	36	4.5	4.5	1.5
10	Har.	24	xylol + toluol			March 12, 1927				52.5	0.5	2.5	0	35.5	7.5	0.5	1
			+10% benzol	7		April 4, 1927	4,750,000	80	6,200	47.5	3.5	3	2	37.5	3.5	2	1
11	Fi.	30	xylol + toluol			March 12, 1927				64	2	1.5	0	23	5	2.5	2
			+10% benzol	1		April 4, 1927	4,665,000	90	6,500	62.5	2.5	3	0	25.5	3	2.5	1
12	Mi.	32	xylol + toluol			March 12, 1927				36.5	2	3.5	0.5	46.5	7.5	3.5	0
			+10% benzol	2½		April 4, 1927	5,140,000	90	6,000	38	3	2.5	0	45.5	6	1.5	3.5
13	Schle.	35	xylol + toluol			March 12, 1927				38	2.5	1	0	49	8	1.5	0
			+10% benzol	1		April 4, 1927	4,700,000	95	7,800	49.5	2.5	1.5	0.5	40	3	2	1
14	Fe.	64	xylol + toluol			March 12, 1927				52	1	2	0.5	35	8	1.5	0
			+10% benzol	12		April 4, 1927	4,960,000	95	6,100	58.5	2.5	4.5	1	27	2	3.5	1
15	Bo.	59	xylol + toluol			March 12, 1927				46.5	0.5	2.5	0	42	3	2.5	3
			+10% benzol	11		April 4, 1927	5,820,000	95	27,450	50.5	1.5	2.5	0.5	34.5	4	5.5	1
16	Fu.	25	xylol + toluol														
			+2% benzol	1		May 25, 1926				38.5	0	6	1	46	6	1	1.5
			xylol + toluol			March 12, 1927	.....	...	.....	43	0	4.5	0.5	47.5	2	2.5	0
			+10% benzol														
17	Pl.	46	xylol + toluol														
			+2% benzol	31		May 25, 1926	.....	...	.....	34	1	4.5	0	34.5	21.5	3.5	1
18	Ko.	44	pure benzol	5 mos.		July 1, 1927[2]	.....	...	.....	44.5	1.5	4.5	0	32	13.5	4	0

[1] Dr. Teleky has supplied this translation for *Stabkernige* of the German. He calls attention to the fact that these cells are not transitionals.

[2] April 11, 1927, acute, moderately severe benzol poisoning; buzzing in the ears, headache, nausea, and spots before the eyes. At the time of the blood examination, no symptoms of illness appeared.

was present. Throughout there was a pronounced and considerable lymphocytosis. The normal lymphocyte count of 21 to 25 per cent. was exceeded in practically all cases, the count for the small lymphocytes alone being increased to 35 to 40 per cent. in most instances. As a further important finding a concomitant increase in large lymphocytes must be noted. This was present in nearly all cases and in one case (No. 17) was of unusually high grade, 21.5 per cent. This increase in large forms can unquestionably be considered to indicate a stimulation for their formation. This is especially so if one thinks of them as young forms and their increased number as expressing a premature appearance of unripe elements due to strong demands on the parent tissues. This conception was confirmed by the frequent occurrence of large lymphocytes with double nuclei or dividing nuclei, also a sign of increased production of nongranular white cells. Finally, the invariable presence of plasma cells speaks for a stimulation of the nongranular system of leukocytes. Plasma cells or Türck's stimulation forms are considered to be immature cells damaged in their development. They are not found in normal blood in adults. Their origin is still debatable—lymph glands or reticulo-endothelial system—but in any case they behave as do the lymphocytes (for example, in German measles) and must be considered as pathologic cells of the lymphatic system.

Corresponding to the increase in lymphocytes, there was a decrease in neutrophil leukocytes; a slight displacement to the left (Arneth) in single cases must not, however, be given much significance since it rests in normal bounds. Eosinophilia was never found. The platelets were normal in number and shape. In a few preparations a number of large forms with thick, dark chromatin particles and pale edges were found.

The changes in the blood picture consisted then, in the main, of a lymphocytosis, with the appearance of immature and pathologic cells of the nongranular series. *These changes appeared with equal readiness from the action of pure benzol and from the combined effect of xylol, toluol, and benzol.* Indeed, one can establish, rather, an increased tendency for the appearance of these cells as a result of inhaling the mixture of aromatic compounds. At any rate one can find for xylol and toluol an action on the blood cells equal to that of the benzol alone, since the small quantity of benzol in the mixture of solvents is not capable of distorting the blood picture.[1] The percentile composition of the blood is thus found to be a more sensitive indicator of blood changes following chemical irritation than are the absolute counts of blood cells. According to the American investigations the absolute counts would not have indicated the effects of xylol and toluol since they had undergone no significant variation. The differential count, on the other hand, discloses the characteristic shift to the lymphatic side. It must therefore be viewed as the dominant investigative means for recognition of damage, and for

[1] In spite of the lower boiling point of benzol, its share in the room air in relation to the large amounts of xylol and toluol can be but slight.

judging the danger to the body from absorption of the aromatic compounds.

Naphthalene

The blood changes in benzol poisoning—the lymphocytosis and anemia—give occasion to mention an analogous type of blood damage due to naphthalene. I have observed a clinical instance of this and have obtained verification of my findings by animal experiment (10). Naphthalene ($C_{10}H_8$) is formed from two condensed benzol nuclei and this accounts for its analogy to benzol in the effect on the blood. In pronounced naphthalene poisoning a destruction of erythrocytes very similar to that caused by benzol is recognized, and even earlier the similarity to benzol action is closely approached. The motive for the animal experiments was given by a case of acute lymphatic leukemia in which the question of subchronic naphthalene poisoning due to the long-continued taking of small quantities of naphthalene (for the purpose of getting rid of Oxyuris) arose. Since all the other causative factors of leukemia—pregnancy, tumor, infection, and parasitic disease—could be excluded, the idea of naphthalene was forced into prominence.

In young dogs it was found that beside the well-known symptoms of poisoning—vomiting, emaciation, and bloody and bile-stained urine—one could produce a severe anemia with anisocytosis, poikilocytosis, normoblasts, megaloblasts, and a leukemia with pronounced lymphocytosis. The leukocyte count rose from 5,800 to 14,200 per cubic millimeter. The extreme neutrophil blood picture of the dog gave place to a very definite leukocytosis with marked lymphocytosis and the appearance in the blood stream of immature cells of both granular and nongranular systems, myelocytes and plasma cells. The question as to the provocative action of naphthalene could then be answered. An organ predisposed to disease receives from naphthalene a stimulus for increased formation of lymphocytes which becomes excessive and eventually reaches a pathologic level. Thus a simple lymphatic reaction can apparently degenerate into a leukemic state.

The literature supplies a second case of fatal blood disease due to toluol, xylol, and benzol, with naphthalene identified as the deciding if not the causative factor in the production of the anemia. Heubner (11) has described the illness of a workman who had worked eight hours asphalting the floor of a ship's hold which had previously been tarred, a procedure liberating tarry fumes and leading to the inhalation of naphthalene, xylol, toluol, and other benzol derivatives. After finishing the work he complained of cough, substernal oppression, vertigo, breathlessness, and nausea which progressed to vomiting. During the following weeks there was increasing dulness, weakness, dyspnea, and a general decline. Swelling of the legs and feet, and jaundice ensued. After five weeks the man reported himself as sick. Two weeks later aplastic anemia was established and death occurred in eight days more. Heubner is inclined to ascribe to the tar fumes an essential and decisive part in the rapid course of the disease, in spite of the brief duration of exposure (on account of the possibility

of after effect). He does not even reject the possibility of the causation of fatal anemia by the aromatic poisons. Aplastic anemia is the expression of the most extreme stage of the destructive action of benzol and its homologues on the blood forming tissues. At the same time such an anemia shows a shifting of the benzol effect from the leukocyte forming tissues, which are ordinarily the chief site of attack, to the erythropoietic centers. *An unusually high sensitivity to the poison and an especial susceptibility of the erythrocytic centers must be thought of as contributing to the explanation of the destructive action of the poison.*

To what different disease pictures these individual differences in disposition and susceptibility can lead may be shown by a third case from our own experience. To be sure, this case cannot be placed with the others unreservedly since only small amounts of aromatic bodies were absorbed and the action of the poisons cannot be proved with surety. A workman, at his task, had opportunity over several years' time to inhale tar fumes. He became ill with a subacute myeloid leukemia, fatal in five months, of aleukemic type with very low leukocyte count—only 2,300 per cubic millimeter. This was coupled with a severe anemia which assumed pernicious characteristics. If one ascribes to the aromatic poisons a share in the causation of the disease, one must conceive that in this instance the poisons produced a depression of the whole blood forming apparatus with a stimulation of the myeloid centers in contrast to the stimulation of the lymphatic centers described in the case of lymphatic leukemia mentioned above. The site and severity of the effects observed seem to depend not so much on the amount and type of the poison as on the peculiar susceptibility of the victim. Perhaps we must also grant to the specific reaction of the body, as well as to the specific action of the poison, a part in the special type of blood disease which appears.

Nitro Compounds

In another factory workers were required to handle large cakes of dinitrobenzol, trinitronaphthalene, and other aromatic nitro compounds. Although the work continued for only an hour at a time and did not occur every day, a number of the men fell sick quite promptly, within one to three weeks, with typical symptoms of methemoglobinemia—breathlessness, cyanosis, dizziness, headache, dulness, and jaundice. One group was compelled to stop work entirely. The remainder continued handling the dangerous material, but not every day and for only a few hours in the day. Both groups were examined. (See Table 4.)

From the very first there was a fundamental difference in the findings on the men kept at work and on those removed. During work with the nitro compounds a lymphocytosis developed, with marked increase in large forms and appearance of abnormal cells. In one instance (workman Gör., No. 1) there was an outright reversal of the usual leukocytic formula, the neutrophil cells comprising but 30.5 per cent. and the lymphocytes 55.5 per cent. of the total count. After withdrawal from

work the extreme lymphocytosis disappeared almost with the sureness of a laboratory experiment. Slightly increased counts remained stubbornly over weeks of time; in one case, No. 7, after forty days the lymphocyte count had not reached a normal level. It should be pointed out that, directly this worker fell ill after short employment with the dangerous chemicals, he had pronounced subjective ailments and could not recover for a long time. He was suspected of simulation or aggravation. The true significance of these symptoms could be appreciated when the blood picture as expressing objective damage was compared with the subjective symptoms. The blood picture might thus be very well adapted in similar cases

TABLE 4.—BLOOD FINDINGS FOLLOWING ABSORPTION OF AROMATIC NITRO COMPOUNDS

NUMBER	NAME OF WORKMAN	AGE yrs.	DURATION OF WORK days	LENGTH OF TIME AFTER LEAVING WORK days	SYMPTOMS	DIFFERENTIAL LEUKOCYTE COUNT							
						Polynuclear Neutrophils %	Staff-like Neutrophils[1] %	Eosinophils %	Basophils %	Small Lymphocytes %	Large Lymphocytes %	Monocytes %	Plasma Cells %
In Men during Employment													
1	Gör.	37	10	..	dizziness, headache, cyanosis	30.5	0	4	0.5	41	14.5	8.5	1
2	Au.	35	21	..	pronounced cyanosis, icteroid hue, headache	32	0	4.5	1	38	12.5	9	3
3	Kirm.	30	21	..	pronounced cyanosis, jaundice, headache	49.5	2	2.5	1	34.5	7.5	3	0
4	Oes.	58	21	..	pronounced cyanosis, severe jaundice; looks ill	36	1	5.5	2	41	7	5	2.5
In Men after Removal from Work													
5	De.	25	5	15	still sick; substernal oppression, headache	56.5	2.5	2	0	26.5	7	4	1.5
6	Dum.	53	21	18	cyanosis, weakness in the legs	58	1	6	2	29	1	3	0
7	Grie.	33	8	40	still some cyanosis	54	2.5	2	0	38.5	2	1	0
8	Pau.	59	10	36	cyanosis, low blood pressure	70.5	7	1	0	17.5	2	2	0

[1] See footnote 1, Table 3.

to show the duration of the damage. In all the workmen the red blood cells were not much changed and the platelets showed no variation from the normal. The slight damage suffered from the aromatic nitro substances had thus altered the lymphatic system alone.

Let us now review two other cases, men from similar employment, who were exposed to the chronic action of nitro compounds of the aromatic series and who suffered a severe to fatal damage of the erythropoietic system. Their illness can be compared with the fatal anemia of the English trinitrotoluol workers to which reference has been made (8). Both developed a fatal pernicious anemia. One had been employed for eighteen years as a mason in a large chemical factory and quite frequently worked in the aniline department. He became ill and complained of dulness, weakness, and loss of vigor with the early development of pernicious anemia which, with the usual remissions and exacerbations, led to death after two years. Shortly before death the blood showed the following:

Hemoglobin	33–35%
Erythrocytes	1,160,000
Color index	1.4
Leukocytes	1,200

Red blood cells: anisocytosis, poikilocytosis, stippled erythrocytes; no normoblasts.

Thirteen days later the findings were:

Hemoglobin	28–30%
Erythrocytes	967,000
Color index	1.4
Leukocytes	4,200

The second man had worked with trinitrotoluol from 1916 to 1919, from 1919 to 1920 principally with dinitrobenzol, again for two months in 1923 with trinitrotoluol, and in the final months of 1924 with nitroglycerin. (Injury to the blood from nitroglycerin is not as yet an established fact. The work with nitroglycerin cannot, therefore, be considered answerable for the disease.) In the beginning of 1925 the patient experienced loss of appetite and of strength. Work was stopped in the following April and soon the symptoms of pernicious anemia showed themselves. Death occurred a year later in May, 1926. The blood shortly before death showed the following:

Hemoglobin	34%
Erythrocytes	1,060,000
Color index	1.6
Coagulation time	1.75 min.
Leukocytes	3,300
Platelets	132,000

Red blood cells: pronounced anisocytosis, poikilocytosis, polychromatophilia, depressions.

7 normoblasts 1 megaloblast 31 polychromatophils 11 basophilic granular cells	in 200 white cells

White blood cells:	
Neutrophils	32.0%
Young forms	2.5%
Staff-like neutrophils[2]	3.0%
Degenerating neutrophils	3.0%
Eosinophils	4.0%
Small lymphocytes	54.5%
Large lymphocytes	1.0%

From the beginning of illness to the final action of the nitro compounds there was such a long latent period that it may appear questionable as to whether a causal relation can be found between the absorption of the

[2] See footnote 1 Table 3.

poisons and the origin of the anemia. Similar observations from English literature may, however, be considered. Just such anemias after ceasing work are described in workmen with nitro compounds, and these took place after a long and symptomless latent period. The English authors without more ado ascribe the anemia to the influence or after effect of these poisons. O'Donovan (8, p. 73) refers to seven cases of anemia, in which there were three of aplastic fatal type, all of which became manifest either weeks or months, in one instance six months, after acute trinitrotoluol poisoning. In some cases cyanosis and jaundice, which ordinarily appear as onset symptoms during or immediately after removal from work, came long after removal from the operation. Barnes (8, p. 84) explained the delayed action of trinitrotoluol as a storage of the substance in the body which later produced symptoms. Rolleston (8, p. 102) postulated liver damage. Similar delayed action must account for the anemia in our cases.

Arsine

Acute poisoning with arsine (AsH_3) in seven men from one factory gave opportunity for the following blood studies. The men sickened with severe and moderate symptoms of poisoning, vomiting, jaundice, hematuria, and pain in the kidney region. One died the day after the poisoning took place. Five were observed five days after the onset. The blood findings were apparently identical (see Table 5). All had the same shifting to the lymphocytic side in the differential blood picture. All showed a slight tendency toward eosinophilia. For various reasons absolute counts of leukocytes and erythrocytes were not made.

Our findings contribute a confirmation and amplification of the change in blood picture found by Dudley (12) in thirty sailors from two submarines. These men had inhaled arsine and fell ill with gastro-intestinal and especially with neuritic symptoms. They were examined after five days or more, a period identical with that involved in the case of our own workmen. All gave the same changes, first of all a lymphocytosis of significant degree. This reached 50 to 71 per cent. and, according to Dudley's view, could have permitted a diagnosis of leukemia. The lymphocytosis became maximum in the second week after the poisoning occurred. (Apparently we might have found a higher lymphocytosis in second and third week preparations from our patients also.) The eosinophilia discovered by us is a confirmation of Dudley's finding, as is also the displacement to the left in the Arneth count. The most striking and most alarming symptoms of blood damage were a decrease in erythrocytes to below 2,000,000 per cubic millimeter, and a hemoglobin reduction to 50 per cent. With these findings there was an increase in the resistance of the erythrocytes to hypotonic sodium chloride solution. Dudley placed this anemia in the foreground of the whole disease picture, speaking of the poisoning as "toxic anemia from arseniuretted hydrogen gas." Two of Dudley's cases were especially prominent as

TABLE 5.—BLOOD FINDINGS FOLLOWING ABSORPTION OF ARSINE

NUMBER	NAME OF WORKMAN	AGE	SYMPTOMS	INTERVAL BETWEEN ONSET OF ILLNESS AND BLOOD EXAMINATION	ERYTHROCYTES	DIFFERENTIAL LEUKOCYTE COUNT							
						Polynuclear Neutrophils	Staff-like Neutrophils[1]	Eosinophils	Basophils	Small Lymphocytes	Large Lymphocytes	Monocytes	Plasma Cells
		yrs.		*days*		%	%	%	%	%	%	%	%
1	Ka.	..	severe poisoning; headache, vomiting, enlargement of liver, pain in kidney region, jaundice, hematuria	5	not changed pathologically	49.5	4	5	0.5	35.5	4	1.5	0
2	Wei.	about 25	moderately severe poisoning; headache, vomiting, jaundice, hematuria	5	3 nucleated normoblasts in 200 white cells	44	3.5	6	1	38	5	2.5	0
3	We.	..	moderately severe poisoning; symptoms as in No. 2	5	normal	48.5	3	2	0	37.5	7	2	0
4	Bac.	..	moderately severe poisoning; symptoms as in No. 2	5	6 normoblasts in 200 white cells	58.5	2.5	1	0	32.5	4.5	1	0
5	Za.	57	moderately severe poisoning; symptoms as in No. 2	5	normal	56.5	8	0	0	27.5	5	3	0
6	Haa.	..	severe poisoning; stupor, dizziness, vomiting, thirst, conjunctivitis	several months	slight anisocytosis	47	2.7	5.3	0.3	40	2.3	2	0.3

[1] See footnote 1, Table 3.

displaying the irritative and degenerative action of arsine on the blood forming centers. Two of the patients, who were examined two days after leaving the submarine, had the blood picture of pernicious anemia, red cell counts of 1,980,000 and 2,720,000, hemoglobin of 66 and 52 per cent., a color index of 1.2 together with poikilocytosis, anisocytosis, basophilic stippling, polychromatophilia, normoblasts, megaloblasts, and a dark yellow, bile-stained serum. The other symptoms in both patients were no more severe than in the other sailors, as generally blood changes and general symptoms did not run parallel. The blood retained the characteristics of pernicious anemia for but a few days, and with the general bodily recovery the blood picture returned to normal. It is possible therefore that other men in the group might have displayed more severe damage to the blood had an earlier examination been made. At any rate the findings showed how severely arsine can alter the blood, and established the possibility of initiating a pernicious anemia, also due to arsine, through persistence of the blood destroying effect in susceptible persons.

For this conception an appropriate case of pernicious anemia can be contributed, a case which probably had acute arsine poisoning as the initiating factor. A formerly healthy man became ill immediately after inhaling arsenical dust. He presented the following symptoms of poisoning: dizziness, scratchy throat, inflammation of the eyes, nausea, and tormenting thirst. The later disease picture consisted of somewhat changing gastrointestinal symptoms, vomiting, pain, and hematemesis, together with nervous troubles, paresthesias, numbness in the arms and legs, itching sensations over the entire body, furunculosis, and ulceration of the mucous membranes. During the ensuing months these symptoms never entirely disappeared, in spite of constant medical treatment and temporary returns of ability to work. The condition gradually became worse, and after a year the diagnosis of pernicious anemia was made. In the blood picture, besides the typical signs of pernicious anemia, a pronounced lymphocytosis, 55 per cent., must be mentioned. A year and three-quarters later the patient came to a hospital. He was very cachectic, and ten days before death had the following blood picture:

Erythrocytes	1,900,000
Leukocytes	6,200

Smear: poikilocytosis, anisocytosis, polychromatophilia, megalocytes.

Autopsy confirmed the diagnosis of pernicious anemia.

If we permit ourselves to conjecture a causal relation between the arsine poisoning and the outbreak of the anemia, which it must be admitted cannot be done with entire safety in view of our lack of knowledge of the etiology and pathogenesis of pernicious anemia, we can find some confirmation for our supposition in the continuity of the symptoms from the day of the poisoning until the death of this formerly healthy and hard-working man.

Thallium

A series of examinations were also undertaken in thirteen men exposed to the action of thallium. A striking

type of damage, rapid reduction of vision in one of these men, gave impetus to the investigations. The condition involved a 19-year old man who had been at the thallium work for five months and who had no antecedent signs of illness.

Ophthalmologic Examination.—Right eye, no conjunctivitis, vision 2/60; emmetropic, externally normal. Iris: on the temporal side the posterior portion is adherent to the anterior part of the lens capsule. From this adherent area there extends an opacity of the lens which becomes less in the depths of the lens. Fundus: papilla borders indistinct, temporal sharp. Veins distended a little. Temporal half of the papilla pale. Visual field free peripherally. Total central scotoma, relative for green and red. *Left eye,* no conjunctivitis, vision 2/60; emmetropic, externally normal. Lens and cornea clear. Pupil, medium sized, round, and reacts promptly to light and convergence. Fundus: papilla, as on the right side. Visual field, peripherally and centrally like the right.

The ophthalmologic diagnosis was postneuritic atrophy. Since other causes were lacking one apparently must raise the question of thallium poisoning. The lens opacity must certainly be held to be due to thallium since in animal experiments thallium was found to cause cataract.

Throat, nose (except for septal deviation), and ears were found normal by a specialist. Wassermann reaction negative. No pathologic findings in the lungs and abdomen.

Among the results of thallium poisoning, reduction of vision has not heretofore been observed. The relation to work in thallium in our case must not be thought to prove it.[3] Other damage due to thallium has been known for a long time. During the early part of the nineteenth century, especially in France, thallium was used as an anhidrotic but was soon given up on account of disagreeable and dangerous secondary effects. More recently thallium has gained further significance through its use as a depilatory (13) and as a rat poison. The sale as rat poison has already led to a murder and several suicides (14) (15).

The symptoms of poisoning in men were pains in the legs, weariness, loss of hair, disturbances of sensation, numbness, psychic troubles, albuminuria, and nephritis. In animal experiments, eye changes were also observed—keratitis, iritis, and cataract.

Buschke and Peiser (13), and also Buschke, Christeller, and Loewenstein (16), employing young rats, were able to produce a developmental and particularly in bone formation a generalized rickets or peculiar bone disease (malacia). They found an alkalosis also and an achlorhydria which they considered a partial expression of the alkalosis. In the blood there was a "transient eosinophilia and lymphocytosis" and both of these could be of considerable magnitude. Redlich found a lymphocytosis of 41 per cent. in a man with a total count of 5,100 leukocytes per cubic millimeter. Buschke and Peiser are disposed to consider the thallium symptoms as the results or signs of an endocrine and sympathetic nervous system disturbance. Experimental results of Zondek (17) appear to give support to this view. They show an influence of thallium on the libido, that is, on the ovarian and hypophysial hormones.

[3] In order to get at the question of damage to the optic nerve, thallium was immediately subjected to trial in the Pharmacological Institute of the Medical Academy, rabbits being the animals used.

The thallium workers we have examined had typical signs of poisoning after three to four months. They complained of fatigue, and of pains in the legs, especially in the knees, which in some cases compelled cessation of work. There was loss of hair in one case and kidney irritation in a number of cases, in two of which nephritis developed in spite of stopping work.

The results of the blood examinations are given in Table 6. A lymphocytosis was found uniformly. Even in a man employed for but four days (worker Cza., No. 10) this tendency to reversal of the leukocyte formula can be recognized. The characteristic blood findings reported in the literature could also be confirmed. (An apparent exception is found in No. 1. But here, on account of visual disturbances, work had been interrupted for a long time.) The lymphocytosis reached a very considerable magnitude. Most of the counts were above 40 per cent. and it appears noteworthy that the highest values, 50 per cent. and over, were found in the men with kidney irritation, although the blood changes did not run directly parallel to the other symptoms. Also, thallium seems to have a secondary effect. At any rate the lymphocytosis endured for some time after the men left work and even increased. Eosinophilia was found in only a few instances, the highest count being in the patient with optic atrophy. Clinically as well as hematologically this case was exceptional.

To amplify the clinical blood studies we have examined the blood of rabbits that have received thallium. Rabbits possess a lymphocytic blood picture normally, with average values of 45 per cent. for the lymphocytes, and 50 per cent. for the neutrophils (see Table 7). Rabbits' blood contains large cells with round reddish or bluish violet granules which seem very similar to basophilic myelocytes and are usually counted as basophils but which correspond more properly to immature eosinophils. Perhaps their occurrence explains the low count of circulating eosinophils in normal rabbit blood. The blood of the experimental animals showed with only one exception a significant lymphocytosis and a slight increase in monocytes. The reaction corresponds to the cell change in human blood in thallium poisoning.

Trichlorethylene

A few investigations on the action of trichlorethylene on the blood of workers gave normal absolute blood counts and a normal relationship in the differential examination.

Cyanide Poisoning

After the disinfection of a large mill with hydrocyanic acid in order to kill meal moths and other grain destroying insects, forty of 200 girls who were working in a large room experienced hydrocyanic acid poisoning two to three hours after resumption of work.

The mill was filled with gas for fifteen and one-half hours and then aired for twenty-one hours. The necessary test for residual gas was made and was found negative—without this it is not permitted, according to the regulations, to resume work. One regulation was neglected—namely, that before making the gas test the windows must be closed for

TABLE 6.—BLOOD FINDINGS FOLLOWING ABSORPTION OF THALLIUM

NUMBER	NAME OF WORKMAN	AGE	DURATION OF WORK	SYMPTOMS	DATE OF BLOOD EXAMINATION	DIFFERENTIAL LEUKOCYTE COUNT							
						Polynuclear Neutrophils	Staff-like Neutrophils[1]	Eosinophils	Basophils	Small Lymphocytes	Large Lymphocytes	Monocytes	Plasma Cells
		yrs.	*mos.*			%	%	%	%	%	%	%	%
1	Le.	19	4 stopped work Feb. 25, 1927	optic atrophy	March 22, 1927	63	3	12	0	15	5	2	0
					March 26, 1927[2]	62	2	8	1	20	5	2	0
2	Her.	51	7 8	.....	March 18, 1927	45	0	2	1	44	5	3	0
3	Ohl.	23	$4\frac{1}{2}$ $5\frac{1}{2}$ 7	in the beginning, fatigue; now well	April 15, 1927	50	0	6	1	35	4	4	0
					March 18, 1927	48	1	3	0	39.5	4.5	4	0
					April 15, 1927	50	2	2	0	44	1	1	0
4	Gren.	17	2 stopped work April 14–May 4, 1927	no complaint kidney irritation	May 27, 1927	34	0	2	0.5	52.5	7.5	3.5	0
					July 5, 1927	45	1	6	0	39	7	2	0
					March 22, 1927	46	0	6	0	40	4	4	0
					May 27, 1927	44.5	1.5	2.5	1.5	42.5	4.5	1.5	1.5
5	Zo.	18	2 stopped work March 28–April 8, 1927	fatigue, pains in knees loss of hair kidney irritation	March 22, 1927	38	1	1	1	53	5	1	0
					April 15, 1927	34	2	2	0	47	8	3	4
					June 10, 1927	41	1	1	0	45	8	4	0
6	Gau.	..	.....	.....	April 15, 1927	49	0	5	0	39	3	4	0

7	Dom.	..	3 stopped work May 7–22, 1927	kidney irritation (May 27, 1927)	April 15, 1927	38	2	5	0	51	3	1	0
					June 10, 1927	27	2	2	0	61	4	4	0
8	Stie.	15	$2\frac{1}{2}$	.....	May 27, 1927	38	0	6	0.5	47	7	1.5	0
					July 5, 1927	45	3	2	1	36	5	6	2
9	Mö.	18	$2\frac{1}{2}$	loss of hair, fatigue, heartburn, reddening of hair	May 27, 1927	31.5	1.5	1.5	0	51.5	10	4	0
					July 5, 1927	50.5	0	5	0	43.5	0	1	0
10	Cza.	18	4 das.	.....	May 27, 1927	50	2	1	0	33	10	4	0
11	Haus.	15	3 stopped work March 10–April 18 and May 7–June 19, 1927	weakness, staggering gait, trembling of eyelids, increased patellar reflex, severe nephritis	March 22, 1927	45	2	2	0	47	3	1	0
					April 15, 1927	50	4	3	0	39	3	1	0
					June 10, 1927	33	2	2	0	45	8	9	1
12	Ja.	18	.....	.....	July 5, 1927	69	2	4	1	17	6	1	0
13	Frei.	17	3 wks.	.....	July 5, 1927	54	0	4	0	36	2	2	2

[1] See footnote 1, Table 3.

[2] Erythrocytes 4,160,000 per cubic millimeter; hemoglobin 84 per cent.; leukocytes 7,600 per cubic millimeter.

an hour. Four hours after the test was made the girls resumed work. A second test eight hours after the first gave traces of the gas in the middle of the large room of the mill in which the women were working but was negative in the neighborhood of the open windows. The possibility of inhaling the gas was thus offered. Besides this the clothing of the women which had been left in the mill could readily have contained hydrocyanic acid. Cloth absorbs this gas very well indeed, and in spite of thorough airing retains the hydrocyanic acid most stubbornly. As a consequence the girls could inhale the gas given off by their clothes and also were endangered by the possibility of absorption through the skin.

The most noteworthy symptoms of the poisoning were headache, vertigo, vomiting, palpitation, in severe cases anginal attacks with severe pain in the cardiac region, indigestion, diarrhea, and polyuria Many fainted and showed confusion on the recovery of consciousness. In the worst cases there was cyanosis, cardiac weakness, and very inadequate breathing. Confusional states, irritability to the point of raving and crying out, and clonic convulsions were not infrequent complications. In two patients a kidney irritation progressed promptly to an acute nephritis.

The acute symptoms of poisoning ceased after a few days but lesser complaints remained for several weeks. Most of the patients complained of fatigue, headache, anxiety, gastric pain, and dizziness on resumption of

TABLE 7.—BLOOD FINDINGS IN RABBITS FOLLOWING SUBCUTANEOUS INJECTIONS OF THALLIUM NITRATE

NUMBER	WEIGHT OF RABBIT	DOSE OF THALLIUM NITRATE (TWICE WEEKLY)	SYMPTOMS	DIFFERENTIAL LEUKOCYTE COUNT[1]					
				Polynuclear Neutrophils	Eosinophils	Basophils	Small Lymphocytes	Large Lymphocytes	Monocytes
	gm.	*mg.*		%	%	%	%	%	%
1	2,890	10	loss of weight	29.5	1.5	1.5	62.5	2.5	2.5
2	2,420	10	loss of weight, loss of hair on neck	19.5	0	4.5	68	4.5	3.5
3	3,150	5	loss of weight, considerable loss of hair	48.5	0	3	45.5	2	1
4	2,400	5	loss of weight	10	0	2	78.5	6.5	3
5	2,870	2	loss of weight	50	0	3.5	29.5	12.5	4.5
Average normal rabbit blood				50.5[2]	1[2]	2.5[2]	35[2]	10.5[2]	0.4[2]
				51.5[3]	0[3]	1.7[3]	37[3]	9.3[3]	0.7[3]

[1] Blood examination was made 6 weeks after the first injection.
[2] After Klieneberger and Carl.
[3] After the author's experiments.

work. In some instances obvious cyanosis persisted for two to three weeks after the acute poisoning.

The blood of twelve severely affected patients was examined eleven to sixteen days after the date of poisoning, and of four patients eight weeks after that date (see Table 8). In almost all—but two exceptions being noted—there was a definite lymphocytosis, not always high but invariably enough to be considered more than a moderate increase. The lymphocyte counts were augmented 10 to 20 per cent. and in one case 30 per cent., and this increase was in general parallel to the severity of the symptoms. In the lightest case, one of the exceptions mentioned above (No. 10, Table 8), no increase in lymphocytes took place, but symptoms of poisoning occurred after seven and one-half hours of work. One of the worst cases with acute nephritis had the highest lymphocytosis which lasted eight weeks after the acute poisoning. In three others, two months after the onset of illness, the reversal of the blood picture was returning to normal or showed a tendency to do so.

The second important change was found in the basophilic leukocytes. Their count was high—1.5 to 2 per cent. in some cases. In only three preparations were basophils absent. The eosinophils showed an occasional increase of more than 4 per cent. without the other two types of cell showing the parallel change which normally occurs in pathologic cases. In view of the absence of other causes for eosinophilia and basophilia—helminthiasis, asthma, eczema, and blood diseases having been excluded—the increase may be ascribed to the poisoning, the more so since a quite similar finding exists in the literature. Hasselmann (18) observed in some hundred workers a small but definite lymphocytosis and high basophil count occurring along with a distinct eosinophilia.

The neutrophils were normal in form and color; in no case did there exist a noteworthy abnormality. The red blood picture differed from the normal only in a slight anisocytosis. The absolute count could not be determined for extraneous reasons, but, according to the investigation of Hasselmann, an increase in the hemoglobin content and in the red cell count occurs along with a normal leukocyte count, so that the blood picture of cyanide poisoning (in accord with the general phenomena of the disease) reminds one of polycythemia rubra.

Discussion and Summary

If one reviews the results of these blood examinations indicating industrial disease due to chemical substances, one finds a certain reaction with the utmost regularity, namely, lymphocytosis with the reversal of the leukocyte formula to the lymphocytic side. Regardless of which poison is acting, whether benzol, toluol, xylol, naphthalene, aromatic nitro compounds, arsine, thallium, or hydrocyanic acid, invariably the lymphocytes show an increased number in the blood stream. The neutrophils are forced back or repressed. This identity of variation makes one think of an identity of causation, and leads one to seek a similar blood reaction in human pathology. There is a group of disease changes which possess the

TABLE 8.—BLOOD FINDINGS IN CYANIDE POISONING

NUMBER	NAME OF WORKER	AGE	SYMPTOMS	INTERVAL BETWEEN ONSET OF ILLNESS AND BLOOD EXAMINATION	DIFFERENTIAL LEUKOCYTE COUNT								REMARKS
					Polynuclear Neutrophils	Staff-like Neutrophils[1]	Eosinophils	Basophils	Small Lymphocytes	Large Lymphocytes	Monocytes	Plasma Cells	
		yrs.		*days*	%	%	%	%	%	%	%	%	
1	Erna L.	17	2 hours after beginning work, unconsciousness, circulatory disturbance, headache, eczema of the face, stupor, and nausea.	14	38	1.3	9.3	0	41.3	5.3	4.3	0.5	History: Without pathologic data.
2	Maria R.	21	After 1½ hours of work, short unconscious spells, nausea. Later, lassitude, palpitation of the heart, gastric pain after eating, anxiety. Slight cyanosis.	14	59	1	3	2	32	2	1	0	History: Slight form of Basedow's disease. Suffered always from restlessness, constipation. Tremor of the hands; slight exophthalmos.
3	Johanna M.	19	3 hours after beginning work, dizziness, headache, nausea, loss of appetite. Headache still persisted 2 weeks later and there was also slight cyanosis.	16	46.5	2.5	4.5	0.5	39.5	5	1.5	0	.....

4	Maria Sch.	23	Unconsciousness after 2 hours of work. After 16 days, still frequent gastric pains, heartburn, lassitude, headache, cough, and slight cyanosis.	16	50.5	1.5	1.5	1	41	3	1	0.5	Strikingly delicate woman. Lungs: over the right apex, harsh breathing, respiratory murmurs.
5	Mrs. Eisa Schm.	32	Shortly after beginning work, unconsciousness, convulsions. After 14 days, still had headache, pressure on the stomach, lassitude. Appetite and sleep good.	14	58	2.5	0	1.5	32	4.5	1.5	0	.....
6	Josephine T.	18	Began with headache, long, deep fainting spells. Twitching in both arms, coarse tremor in both hands, which still persisted 11 days later. There was also cyanosis.	11	48	1.6	4.6	0.6	38.6	2.6	3	0.6	.....
7	Elly F.	23	At first, slight pressure on the stomach. About 8 hours later, nausea, vomiting, diarrhea. 3 days later, only slight headache still remained; otherwise patient felt well.	11	55.5	2.5	4.5	0.5	30	4	2	1	.....
8	Elizabeth H.	17	2½ hours after beginning work, nausea, unconsciousness. After 11 days, still nausea after eating. Gastric pain. Dizziness during work. Pallor. Slight cyanosis.	11	46	0	3	2	41	4	4	0	Systolic murmur over the pulmonary orifice of the heart.

TABLE 8.—*Continued*

NUMBER	NAME OF WORKER	AGE	SYMPTOMS	INTERVAL BETWEEN ONSET OF ILLNESS AND BLOOD EXAMINATION	DIFFERENTIAL LEUKOCYTE COUNT								REMARKS
					Polynuclear Neutrophils	Staff-like Neutrophils[1]	Eosinophils	Basophils	Small Lymphocytes	Large Lymphocytes	Monocytes	Plasma Cells	
		yrs.		*days*	%	%	%	%	%	%	%	%	
9	Elfrieda B.	17	2½ hours after beginning work, nausea, vomiting, crying spells, alternating with fainting. After 11 days, still daily cramps in the stomach. Headache, dizziness, lassitude, pain in right leg, slight cyanosis. Strangury.	11	51	2	5	0	32	7	3	0	Had cramps in stomach once before. Was subject to nocturnal enuresis until she was 10 years old.
				58	52.5	0	3	0	37.5	6	1	0	
10	Hubert G.	20	7½ hours after beginning work, vomiting, dyspnea. 14 days later, still faintness and headache.	14	70.5	1.5	2	1.5	19	2	3.5	0	Always sickly; subject to pneumonia and colds. Sensitive young man.
11	Mrs. Gertrude M.	22	1 hour after beginning work, nausea, fainting, cardiac pains which kept recurring, diarrhea, loss of appetite.	14	51.3	1	1.3	1.3	35	4.6	5.5	0	An especially pale and delicate woman.

12	Francisca Sch.	18	Headache, cramps in the stomach, numbness in the hands and feet; later dizziness, polyuria, constipation. Recovered slowly. 16 days later, still great lassitude and poor appetite.	16	49	1.5	2.5	1	41	4	1	0	Delicate, slender girl; pale. Systolic murmurs over all orifices.
13	Wilhelmine P.	22	2 hours after beginning work, faintness. After 4 weeks nephritis still persisted.	58	36.6	3.6	5.3	0.6	49.6	1.3	3	0	.....
14	Anna J.	18	1 hour after beginning work, nausea, headache, faintness. 19 days later, still feeling of oppression. Pain in the sides; cannot stand long.	56	60.5	1	3	0	30	3.5	2	0	.....
15	Mrs. Anna O.	36	Crying, nausea, loss of appetite, polyuria. After 2 days, normal urination, constipation, faintness, slight headache.	56	54.5	1	5.5	0.5	33	4.5	1	0	.....
16	Helen D.	18	Headache, lassitude at first; later, gastric pain, dyspnea, loss of appetite, crying spells, unconsciousness. Feels dizzy all the time, has headache and dyspnea. Slight cyanosis, hypersensibility. Slow flow of thoughts.	56	60	1.5	5.5	1	21.5	9.5	2	0	.....

[1]See footnote 1, Table 3.

same alteration of the leukocytic formula as the absolutely pathognomonic symptom—endocrine-sympathetic nervous system diseases. All diseases due to functional disturbances of the endocrine glands lead to an advance of the lymphocytes and a retreat of the neutrophilic cells. One can conjecture, therefore, not only for thallium, as has been done by Buschke (13) (16), but also for the other chemical poisons an action on the endocrine glands. As a result of functional disturbances of the endocrine glands we have this reversal of the blood formula. This hypothesis requires the existence of other signs of endocrine disturbance, which are unknown or which possibly have not been looked for or been connected with the symptomatology. It may be advanced from this angle that lately functional disorders of the endocrine glands have been brought into consideration as exogenous factors in the causation of pernicious anemia. Schmidt (19) called attention to the anomalous pigmentation in pernicious cases and sees in this a sign of endocrine hypofunction, a deficiency in the hormone from the adrenal cortex. This lack of an internal secretion should lead to an increase in functional activity of the reticulo-endothelial system which in its turn should result in an augmentation of blood formation. The connection between these processes is so close that the degree of anemia becomes directly proportional to the adrenal insufficiency. If one admits that a relation between endocrine glands and diseases of the blood is at least conceivable, then it becomes possible to consider damage to the endocrine glands as a means of causation of changes in the blood due to industrial conditions.

A second conclusion of general type may be drawn from the findings in the blood—namely, that blood changes may be an early symptom, the only symptom, and the permanent symptom of serious damage.

Finally, from the diversity of the reaction to one and the same injury, one can appreciate the significance of individual susceptibility not only for the degree but also for the type and character of the blood disease under observation.

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METAL FUME FEVER: V. RESULTS OF THE INHALATION BY ANIMALS OF ZINC AND MAGNESIUM OXIDE FUMES*

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INTRODUCTION

THE inhalation of freshly generated zinc oxide fume, in which the particle size averages less than 1 micron, frequently causes in man a transient acute illness variously called brassfounders' ague, casters' fever, spelter shakes, or, better, metal fume fever. The symptoms of a typical attack of this illness begin, a few hours after exposure, with a dryness in the throat and an irritating cough. General lassitude, an oppression in the chest particularly noticeable on deep breathing, coughing, nausea, and occasionally vomiting follow; later headache, backache, pains in the limbs; then a chill followed by a rise in temperature to some 40°C., depending on the severity of the exposure (1). The chill lasts about twenty to thirty minutes, rarely two to three hours. The febrile state reaches a maximum in about ten to twelve hours after exposure to the fume and is usually followed by profuse sweating (2). With the passing of the fever, the patient sleeps soundly. He arises the next morning somewhat debilitated, but returns to normal later in the day.

A characteristic feature of metal fume fever is the pronounced leukocytosis (2) which accompanies the rise in temperature and which usually persists for some thirty-six hours after exposure. During the second day and while the leukocyte count is still high, a normal subject enjoys a certain degree of resistance to zinc oxide fume (3)—that is to say, he can inhale, with little or no temperature increase, a dosage of oxide sufficient ordinarily to produce a marked attack of the fever.

The purpose of the experiments reported in this paper, undertaken in the course of a general study of the hygiene of zinc, was to determine whether or not a characteristic reaction—possibly resembling, perhaps merely analogous to metal fume fever in man—could be produced in animals as a result of the inhalation of freshly generated zinc oxide; and, provided a characteristic reaction of this sort could be established, to determine

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whether or not it would also be caused by the inhalation of other freshly generated metal fume products.

Although clinical descriptions of metal fume fever are legion, we have had, up to within the last year or two, very little illuminating or exact experimental work on the physiologic effects of inhaling zinc fume or on the ultimate cause of the ensuing fever. Murgia (4) allowed animals to inhale crushed calamine and blende, zinc containing ores, but as these ores contained lead, in addition to other non-zinciferous compounds, Murgia's observations are useless as a contribution to the effect, either local or general, of inhaled zinc. For many years, the best experimental work on the subject was that of Lehmann (5) who, in experiments performed in 1906 but not published until 1910, subjected men to the inhalation of burned chemically pure zinc and rabbits to the inhalation of or to the intratracheal injection of zinc compounds. Lehmann's experiments on men included clinical observation of symptoms, temperature, pulse, respiration, etc., physical examination of the subjects, analyses of urine, and chemical determinations of the zinc content of the air breathed and of the urine excreted by the experimental subjects. These experiments presented a good clinical picture of the disease and definitely proved that it may be caused in man by the inhalation of chemically pure nascent zinc oxide. As a result of his observations, however, Lehmann inclined to the view that metal fume fever is not a specific effect of zinc but is, in all probability, due to a foreign protein reaction from the absorption of the body contents either of micro-organisms of the respiratory tract killed by the zinc oxide or of damaged epithelial cells. The close resemblance of the disease picture to that of the illness caused by intravenously injected proteins; the fact that it never occurs from the absorption of zinc by any other route; and, finally, the fact that a similar symptom-complex may ensue from the inhalation of other very finely divided powders—*e.g.*, nascent copper oxide (6) and nascent magnesium oxide (7)—all offer supporting evidence to the idea advanced by Lehmann that the zinc molecule is an incident in, rather than the occasion of, metal fume fever.

Lehmann's animal experiments consisted in blowing zinc oxide by way of a catheter into the larynx or through an opening into the trachea of a rabbit, maneuvers from which no particular trouble arose; or in injecting into the trachea a solution of the double salt of sodium zinc tartrate, from which edema of one lung with a pneumonic infiltration in one lobe developed; or in allowing rabbits to breathe air dense with fog from a spray of a solution of the double salt. None of these experiments were successful in producing metal fume fever, and Lehmann discontinued them as unsatisfactory.

Turner and Thompson (8) of the United States Public Health Service, investigating the health hazards of brass foundries, undertook laboratory studies designed to throw light on the pathology of brass foundrymen's ague. Numerous guinea-pigs were exposed in a small box to the inhalation of freshly made zinc oxide prepared by burning chemically pure zinc. In the single exposure experiments concen-

trations of zinc oxide of about 1,000 to 2,500 mg. per cubic meter were used—concentrations which, in man, would produce violent coughing after a few breaths. A man would be incapable of working more than momentarily in the higher of these concentrations and could see but a few feet in front of him on account of the density of the fume.

Observations were made by Turner and Thompson on the temperatures, respiration and pulse rates, and clinical symptoms of the exposed animals and, following autopsy, pathologic studies were made on the lungs. Single one-hour exposures were employed for the most part, though longer single exposures and daily exposures for nine days were given to a small series of animals. The temperature curves of the guinea-pigs dusted for one hour showed, first, a marked fall below normal (0.1° to 3.3°C.), the lowest point being reached about the third or fourth hour following removal from the exposure cage. Between the eighth and ninth hours, the temperatures rose above normal, reaching the maximum about the sixteenth hour, then falling progressively until the normal was reached at about the twenty-fourth hour. A point worth noting and one commented on by the authors is the fact that the greater the fall and the longer the period of depressed temperature, the less was the subsequent rise in temperature and the shorter the period of time in which it remained above normal. Rapid pulse, returning to normal within sixty-six to seventy-two hours or less, early slow, labored respiration, and later very rapid respiration lasting many hours were characteristic occurrences in the zincked guinea-pigs.

Comparing their observations with figures reported by Lehmann (5) and with observations made by Arnstein (9) on persons exposed to fumes during the casting of brass, the Public Health Service investigators write: "In a general way such records of temperature, pulse, and respiration in man . . . . , correspond with the findings in the animal experiments. It seems that with man, as with the animals, a period of subnormal temperature occurs, and is followed by a rise. The extent and height of the rise seem to vary as widely in man as in the individual experimental animals."

Our experience, on the contrary, has not shown that a period of subnormal temperature precedes the onset of metal fume fever in man. In the course of eleven experimentally induced attacks of the fever (1)—attacks in which the subjects' temperatures rose well over 1°C.—we were unable to find a significant drop in temperature prior to the temperature increase, and are, consequently, of the opinion that the drop in temperature found by Turner and Thompson in animals has no exact parallel in man.

In all cases, the pathologic changes in the lungs of Turner and Thompson's guinea-pigs consisted principally in an infiltration of endothelial cells and polymorphonuclear leukocytes. Cellular exudate, consisting chiefly of polymorphonuclears, was present as a rule in the trachea, bronchi, and bronchioles, the condition in general resembling various grades of bronchopneumonia from a very slight involvement to a definite picture of the disease. The pathologic changes progressed in severity for a few hours, apparently reaching their maximum about the tenth hour. Lungs of

animals killed twenty-four hours after exposure showed that the pulmonary condition had begun to subside; forty-eight hours after exposure there was marked improvement with signs of returning to normal.

Turner and Thompson also report that temperature curves of animals injected intravenously with lung extract showed a striking similarity to the temperature curves of animals inhaling zinc oxide, provided the lung extract curve was set forward about four hours. Here we have, clearly, not a specific effect of lung tissue, but an anaphylactic reaction to the injection of a protein. The similarity of the two curves naturally calls to mind Lehmann's explanation of metal fume fever as a foreign protein reaction.

Experimental Data

The experiments reported in this paper were carried out on cats, rabbits, and rats, placed in a large gas cabinet (10) and subjected for varying lengths of time to atmospheres containing freshly generated zinc oxide fume (1) or freshly generated magnesium oxide fume (7), as the case might be, plus carbon dioxide in a concentration of approximately 10 per cent. We have already reported (11) on the addition of 10 per cent. carbon dioxide to a dusty atmosphere as a successful method of stimulating deep respiration in animals and so forcing inhalation into the alveoli of the dust under investigation. Our early experiments were carried out with very finely divided carbon dust plus 10 per cent. carbon dioxide. The lungs of cats subjected to an atmosphere of this sort for a single exposure of $3\frac{1}{4}$ hours showed at autopsy, both grossly and microscopically, an even general distribution of fine carbon particles throughout the alveoli (11). So effectual was the carbon dioxide in overcoming the normal protective mechanism which animals have against the inhalation of dust, and so satisfactory was the microscopic picture of the dusting occurring in its presence, that we have since made a practice of adding 10 per cent. of this gas to the dust clouds in our metal fuming experiments on animals.

Carbon Dioxide Control

To provide controls for temperature observations in our zinc oxide fuming experiments, four cats in separate cages were exposed in the gas cabinet to air plus 10 per cent. carbon dioxide for fifteen minutes, one, two, and three hours, respectively, each animal being carried out at the end of the desired exposure. Rectal temperatures were taken on the afternoon preceding the experiment, just before introduction into the cabinet, within five minutes after removal from the exposure chamber, and then hourly or oftener for several hours. Temperatures, taken five minutes after removal from the cabinet, showed in two instances—the animals exposed three hours and one hour—falls of 0.6° and 1.1°C., respectively, below what we may call the normal temperature zone of cats (37.8° to 39.8°C.), a zone determined by us in the course of eighty-two observations on twenty normal animals. The lowered temperatures disappeared rapidly, however, both animals being well above the low normal line when the second temperature observation was made thirty to forty-eight minutes following re-

moval from the cabinet. This slight transient fall in temperature is quite different from the greater more prolonged fall following metal fume exposure (see Fig. 3) and is probably to be explained by the reduced metabolic rate which frequently appears in cats subjected to the inhalation of carbon dioxide (12).

Zinc Oxide

In the following zinc oxide experiment, twenty-five animals of different species were exposed in the gas cabinet to an atmosphere of freshly generated zinc oxide plus approximately 10 per cent. carbon dioxide, for from fifteen minutes to $3\frac{1}{4}$ hours. A number and a variety of animals and varying exposures were used in order to determine, if possible, the particular species of animal, if any, most susceptible to zinc oxide inhalation and to establish the approximate length of exposure required to give a characteristic reaction. Twelve cats, three rabbits, and ten rats were used, the animals being confined, in groups of two or three, in individual wire cages standing on racks $2\frac{1}{2}$ to 4 feet from the floor.

Zinc Oxide Fume.—The cabinet, with the animals in position, was filled at 7 A. M. with a zinc oxide fume generated by blowing a gentle stream of oxygen across the surface of zinc heated to its approximate boiling point. The methods used in producing the fume and in estimating the mean concentration over any particular time interval have already been described in detail (1). The estimated dosage—that is, the amount of zinc oxide estimated actually to have been breathed by the animals—has been calculated in much the same way as in our previous determinations on men (1). The average minute-volume of a 3-kg. cat at rest in an atmosphere of air plus 10 per cent. carbon dioxide is approximately 4.1 liters (13). This we have assumed in our calculations to have remained constant throughout the dusting experiments. The actual concentration of zinc oxide in the inspired air fell off gradually from about 600 mg. to 110 mg. per cubic meter in the $3\frac{1}{4}$ hours which constituted the maximum exposure. Both of these factors—change in concentration and abnormally high minute-volume—have been taken into account in our estimations of dosage (Tables 2 and 3).

Clinical Results.—At the end of a desired exposure, the animal in question was carried out of the cabinet by an individual entering for the purpose. Three cats and three rats exposed for $3\frac{1}{4}$ hours were killed immediately for pathologic study of their lungs and for determinations of pulmonary zinc content. Clinical observations, including rectal temperature determinations, were made hourly on nine cats, three rabbits, and three rats for approximately twenty-four hours, and then observations twice daily until these animals were killed for pathologic and chemical study after one, two, and four days. With the exception of two cats which were allowed to survive, the rest of the animals were killed after several days' observation.

When removed from the chamber, the three cats exposed fifteen minutes were very quiet but their breathing was not troubled in any way, nor did they give evidence then or later of

excessive secretion of mucus. They ate nothing, however, during the twenty-four hours following the fuming, though milk was placed in their cages. They were bad tempered when handled but appeared cross rather than actually ill. The cat exposed for forty-three minutes was more markedly affected, while all the rest of the cats as the result of their long and severe exposures were prostrated during the ensuing twenty-four hours. When removed from the cabinet they were shivering and were cold to the touch—a condition which continued for several hours in spite of their being in a very warm room. Excessive mucus dribbled from their mouths, respiration was noisy and in some cases labored, and practically all gave evidence of upper respiratory tract obstruction.

One large old rat died in the exposure chamber after $2\frac{1}{2}$ hours, but later examination of his lungs showed a high degree of caseation, a condition which eliminated him as a valid experimental animal. The rest of the rats were unusually quiet when removed from the chamber but exhibited no marked respiratory distress; they became, however, progressively more lively during the course of the night and even nibbled a few bites of food.

The rabbits, at the conclusion of exposure, were quiet but not prostrated, their noses being notably free from the plugs of zinc oxide and mucus so conspicuous in the nostrils of the cats. As the night wore on, they became more and more lively, eating considerable quantities of carrots, and by morning appeared in excellent shape.

Owing to the complexity of the experiment and to our anticipation of a probable rise in temperature after some hours instead of an immediate fall,[1] no temperature determinations were made until 20 minutes or more after the removal from the cabinet of the animals longest exposed. As a result of this, the animals exposed 15 minutes had been out of the cabinet some 3 hours before temperature determinations were made; the 43-minute animals, approximately $2\frac{1}{2}$ hours; the 1 hour and 8 minute animals, 2 hours; the 2 hour and 11 minute animals, $1\frac{1}{4}$ hours; and the $3\frac{1}{4}$-hour animals, approximately $\frac{1}{2}$ to 1 hour. In terms of our control experiment, any temperature drops due to the inhalation of carbon dioxide alone should, by this time, have disappeared.

With the exception, however, of the three cats exposed fifteen minutes and of one rabbit, all the animals on which observations were made showed rectal temperatures below the low normal (the rabbits very slightly) for the species in question, some very markedly below. The striking thing about this reaction was not only its intense character in the longer exposed animals but, in both cats and rats, its prolonged duration. The following tabulation shows the periods of time required for the temperatures of all cats, except those exposed fifteen minutes, to return to 37.8°C., the low level of the normal zone. No subsequent rises in temperature above the normal zone were observed in any of the animals.

[1] These experiments were performed before the publication of Turner and Thompson's work.

Cat No.	*Length of Exposure*	*Time Required for Return to Low Normal*
	hr./min.	*hr./min.*
4	–/43	4/47
5	1/8	7/35
6	2/11	10/33
10	3/15	10/25
11	3/15	9/10
12	3/15	2/6

The rats and the rabbits especially showed much less clinical effect and a more rapid return to normal than did the cats. Whether this phenomenon was due to the possession by rodents of a respiratory mechanism better adapted for protection against the inhalation of dust, or possibly to the fact that rodents require a greater concentration of carbon dioxide to produce a given respiratory increase than do cats, we are unable to say. It is clear from our chemical data, however, that the rats inhaled less zinc per gram of tissue than did the cats. No zinc analyses were made on rabbits.

In Table 1 may be found the durations of exposure of individual animals; the clinical reactions; the minimum and maximum rectal temperatures during the twenty-seven to twenty-nine hours following the beginning of zinc inhalation; the intervals between exposure and death; and the zinc contents of the lungs of exposed animals in milligrams of zinc per gram of tissue. Table 2 contains the estimated total amounts of zinc inhaled by the cats during the varying periods of exposure, together with the actual amounts of zinc recovered from the lungs (trachea and large bronchi removed) of the animals in question. All zinc determinations are given in terms of metallic zinc. Figures for estimated amounts of zinc inhaled have been arrived at by calculations involving data taken from our zinc oxide settling curves and by the assumption that the average minute-volume of a 3-kg. cat at rest in an atmosphere containing 10 per cent. carbon dioxide is 4.1 liters. This assumption is based on the average of forty-one observations made by one of us with L. A. Shaw (13) on unanesthetized cats confined in a small respiration box, minute-volume being registered by means of a delicate plethysmograph connected with an accurate recording device. Nine different animals were employed and the experiments in question carried on for a year, during which time the cats became thoroughly accustomed to the procedure and endured it without struggle or obvious excitement.

The discrepancy evident in Table 2 between the estimated amounts of zinc inhaled and the actual amounts recovered from the lungs of cats killed immediately after exposure is an indication of the very considerable fraction of zinc which either is inhaled and promptly exhaled, or is caught in the upper respiratory passages, to be later coughed up or swallowed, and never reaches the lungs at all—a fraction which probably increases as exposure continues and as the secretion of mucus and the consequent formation of plugs of zinc oxide and mucus become more extensive.

Autopsy Findings.—The lungs of all the animals killed immediately after exposure to zinc oxide fume—three cats and three rats—showed grossly large scattered grayish areas with clear lines of demarcation, for the most part, between the normal pink

lung and the more grayish tissue. With the exception of one cat in which a trifling degree of generalized leukocytic migration into the alveoli was evident, histologically the lungs of these animals were normal.

Grossly, the lungs of animals killed the day following fuming showed the

TABLE 1.—SUMMARY OF DATA ON ANIMALS SUBJECTED TO THE INHALATION OF ZINC OXIDE FUME PLUS 10 PER CENT. CARBON DIOXIDE

ANIMAL NO.	LENGTH OF EXPOSURE	CLINICAL REACTION FOLLOWING EXPOSURE	RECTAL TEMPERATURES DURING 27 TO 29 HOURS FOLLOWING BEGINNING OF EXPOSURE		TIME BETWEEN EXPOSURE AND DEATH	ZINC CONTENT OF LUNGS PER GRAM OF TISSUE
			Minimum	Maximum		
	hr./min.		*°C.*	*°C.*	*days*	*mg.*
Control			normal range[1]			
Cats	–/–	....	37.8	39.8	....	0.015
Zincked						
Cat 1	–/15	mild	38.0	38.9	not killed	....
Cat 2	–/15	mild	38.2	39.0	not killed	....
Cat 3	–/15	mild	38.2	39.1	1	0.250
Cat 4	–/43	moderate	37.4	39.2	1	0.760
Cat 5	1/ 8	severe	35.9	39.2	1	0.719
Cat 6	2/11	severe	35.1	39.4	1	0.500
Cat 7	3/15	....	....	....	killed at once	1.612
Cat 8	3/15	....	....	....	killed at once	1.400
Cat 9	3/15	....	....	....	killed at once	lost
Cat 10	3/15	severe	35.1	38.6	1	1.803
Cat 11	3/15	severe	34.5	38.3	2	0.562
Cat 12	3/15	moderate	37.7	38.5	4	0.012
Control			normal range (14)			
Rats	–/–	....	37.5	38.5	....	0.024
Zincked						
Rat 1	1/ 8	mild	35.1	38.0	2	0.050
Rat 2	2/11	mild	34.1	36.9	2	0.032
Rat 3	3/15	....	....	....	killed at once	0.395
Rat 4	3/15	....	....	....	killed at once	lost
Rat 5	3/15	....	....	....	killed at once	0.373
Rat 6	3/15	mild	....	....	1	0.033
Rat 7	3/15	mild	....	....	2	0.017
Rat 8	3/15	mild	33.8	37.9	4	0.013
Rat 9	3/15	mild	....	....	5	lost
Control			normal range (15)			
Rabbits	–/–	....	38.3	39.9	....	....
Zincked						
Rabbit 1	1/ 8	very slight	38.3	39.9	1	....
Rabbit 2	2/11	very slight	38.2	39.9	1	....
Rabbit 3	3/15	very slight	38.2	39.9	1	....

[1] Derived from our own observations.

same grayish areas noted in the animals killed immediately and, in addition, varying amounts of congestion. Histologically, varying degrees of peribronchial leukocytic infiltration were evident and, within the bronchi, varying amounts of exudate composed almost entirely of polymorphonuclear leukocytes. In some cases, this exudate was almost entirely absent; in others, it was very considerable in amount. Occasionally, a few leukocytes and a few round cells were evident in the alveoli. In two cases, there were patches of solidification. The more marked changes from normal occurred in the lungs of the cats, the rat and rabbit lungs either being entirely normal or showing changes indicating a very mild irritation.

TABLE 2.—ESTIMATED DOSAGE[1] OF CATS INHALING ZINC OXIDE FUME COMPARED WITH AMOUNTS OF ZINC ACTUALLY RECOVERED FROM LUNGS

CAT NO.	WEIGHT	LENGTH OF EXPOSURE	ESTIMATED AMOUNT OF ZINC INHALED	ACTUAL AMOUNT OF ZINC RECOVERED FROM LUNGS	TIME BETWEEN EXPOSURE AND DEATH
	kg.	*hr./min.*	*mg.*	*mg.*	*days*
3	4.3	–/15	36	6.75	1
4	2.7	–/43	59	19.00	1
5	2.8	1/ 8	83	15.10	1
6	3.1	2/11	142	12.80	1
7	2.9	3/15	165	27.40	killed at once
8	3.2	3/15	182	21.00	killed at once
10	2.7	3/15	152	31.20	1
11	2.6	3/15	148	23.60	2
12	2.3	3/15	131	0.53	4
Average normal.....	....	–/–	....	0.35	....

[1] Dosage estimated on basis of actual weights of animals.

The lungs of Cat 11, exposed for $3\frac{1}{4}$ hours and killed after two days, showed several fair-sized areas of complete solidification with a considerable degree of leukocytic infiltration into the alveoli. The bronchi in general contained large amounts of leukocytic exudate but the bronchial mucous membrane was in good condition. In none of the sections did it appear, in this or in other cases, as if the leukocytes in the bronchi were migrating through the bronchial walls. The exudate appeared to have its origin in the alveoli.

Grossly, the lungs of Cat 12, also exposed $3\frac{1}{4}$ hours and killed four days after fuming, were those of lobar pneumonia. Histologically, the tissue was almost wholly solid with an intensely leukocytic exudate and a good deal of blood. The bronchi, however, were almost wholly free of exudate.

A rat killed five days after fuming

showed a moderate leukocytic infiltration with very little exudate in the bronchi.

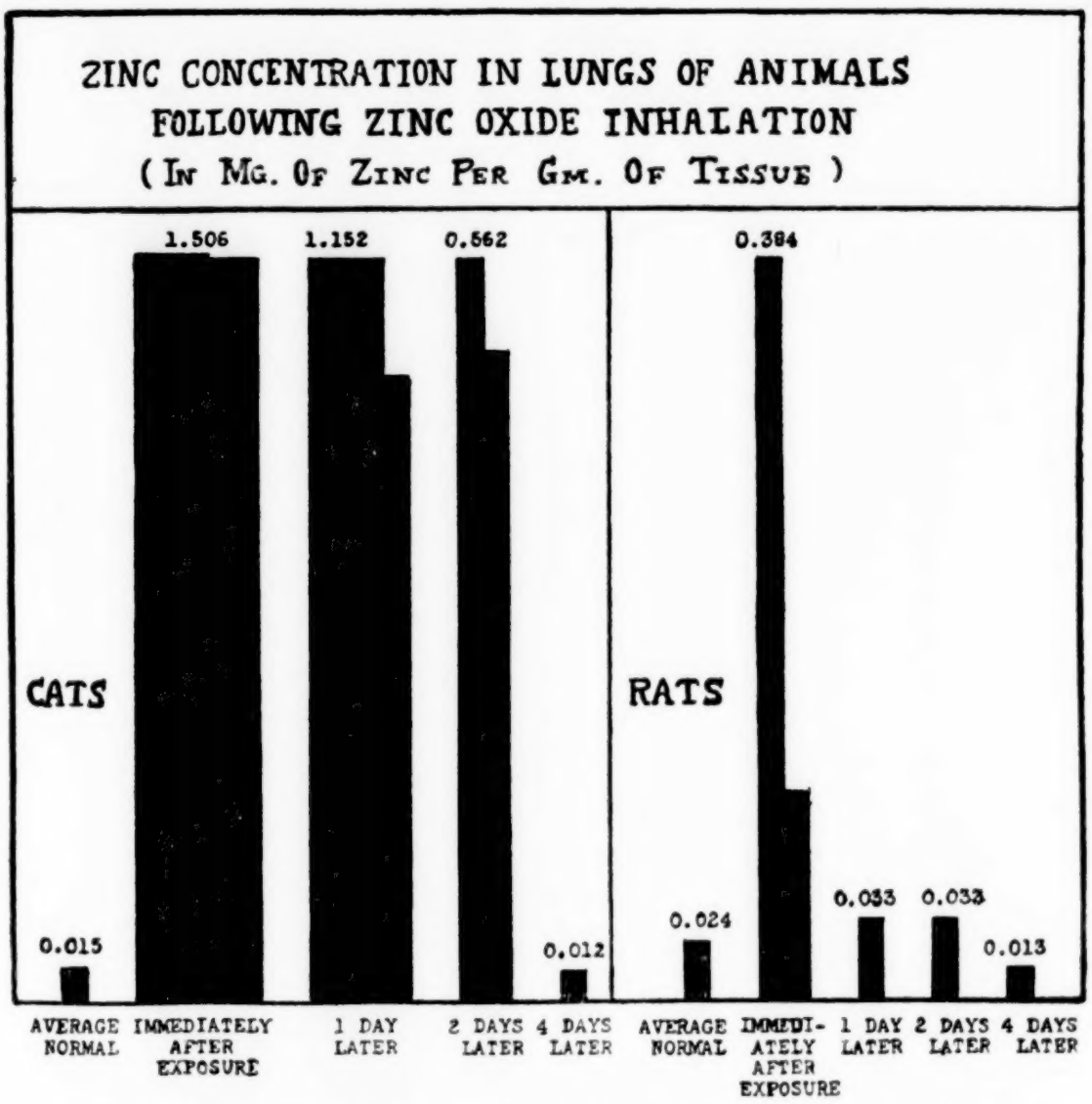

FIG. 1.—Average zinc concentrations in the lungs of cats and of rats killed at intervals during four days following prolonged single exposures to the inhalation of zinc oxide plus 10 per cent. carbon dioxide. Concentrations of zinc are indicated by the total areas of the columns, the actual concentration figure being given at the top of each column. Note the rapid disappearance from the lungs of inhaled zinc.

In summary, we may say that exposure to zinc oxide fume causes a heavy outpouring of polymorphonuclear leukocytes—a reaction to which there is a definite latency. In severely exposed animals, especially cats, the irritative process may go on to a bronchopneumonia.

Chemical Findings.—All zinc analyses in this series of experiments were made by R. E. Lutz. The procedures followed have already been described by Lutz (16) and by Fairhall (17) and may be found in detail in their papers.

Our interest in the chemical findings in our animals inhaling zinc oxide fume centered on the amounts of zinc actually reaching the lungs during varying periods of exposure, on the rate of disappearance of this zinc, and on the concentrations of zinc in the organs involved in its excretion during the early days following fuming. The zinc concentrations of the lungs of all the animals, together with the durations of exposure and the intervals until death, are listed in Table 1. In Figure 1 are plotted average zinc

concentrations in the lungs of cats and of rats killed at intervals during the four days following fuming. All animals included in these averages had been exposed three hours and fifteen minutes, with the exception of one cat and one rat exposed two hours and eleven minutes and one rat exposed one hour and eight minutes. Since the lungs of these latter animals contained amounts of zinc approximate to those of the animals exposed for a longer time, it was considered fair to include them in the averages.

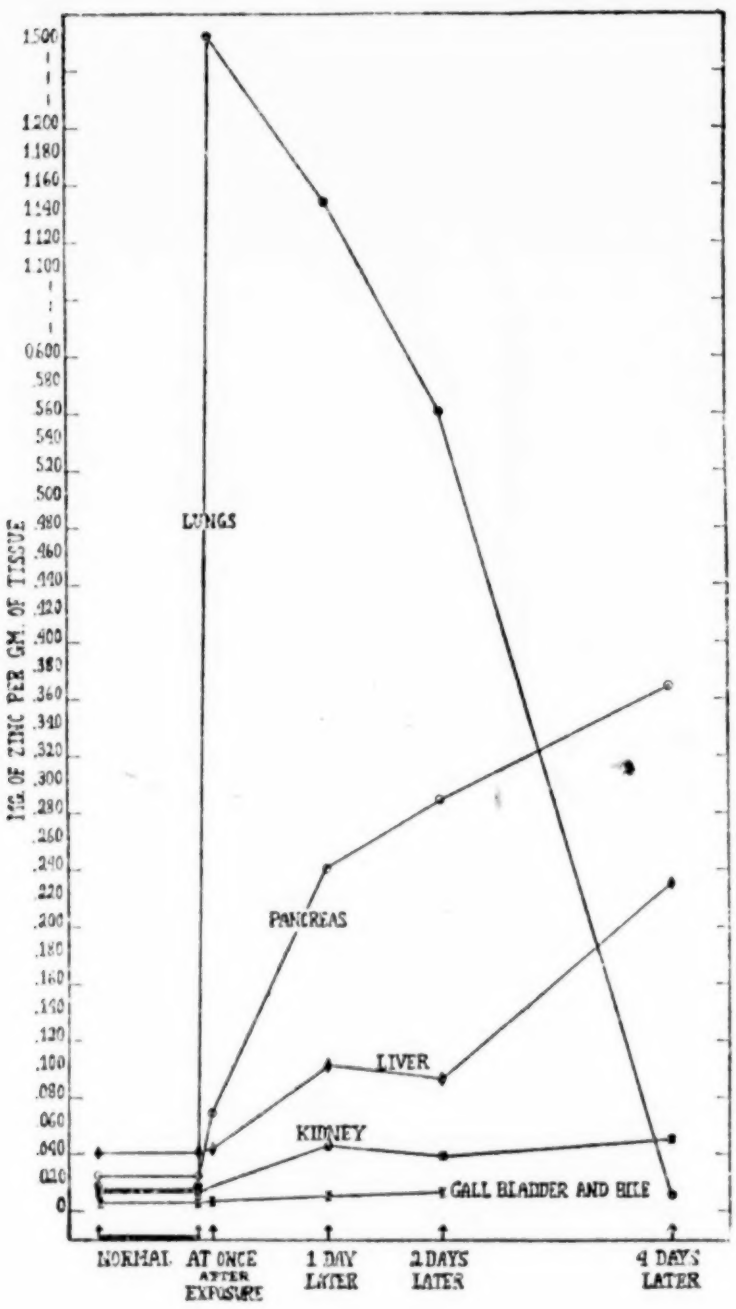

FIG. 2.—Average zinc concentrations in certain cat organs during four days following single prolonged exposures to the inhalation of zinc oxide fume plus 10 per cent. carbon dioxide. See text for comment.

From Table 1 and Figure 1, the following facts may be derived: In a given exposure, cats will inhale proportionately more zinc than will rats; the amounts of zinc inhaled do not vary directly with the length of exposure but are proportionately much greater during the first fifteen to forty-five minutes; inhaled zinc oxide, even in large amounts, is rapidly removed from the lungs of animals, four days sufficing in both our severely exposed cats and rats for complete removal of the abnormal zinc.

Our studies on zinc excretion in zinc fed cats, dogs, and rats (18) (19) have shown that a small fraction of the ingested zinc leaves the body in the urine but that the main bulk of it is excreted into the alimentary tract—some of it directly, some of it by the liver into the bile, and possibly some of it by the pancreas—and ultimately leaves the body in the feces. In zinc fed animals, the zinc concentrations of organs involved in this excretion (liver, gallbladder and bile, gastrointestinal tract and (?) pancreas) are increased as a result of the zinc oxide ingested, but these abnormal concentrations rapidly fall to the normal level when zinc dosing is discontinued. The same phenomenon is evident in animals inhaling zinc oxide instead of ingesting it. As zinc is removed from the lungs and its concentration there diminishes, the zinc concentrations of the liver, gallbladder and bile, kidney, and, interestingly enough, the pancreas rise. In Figure 2, these shifts in concentration are plotted graphically from analyses on the organs of seven severely exposed cats. Because

of contamination from zinc coughed up and swallowed, no analyses were made on the gastro-intestinal tract.

Magnesium Oxide

In the following experiment, six cats were exposed in the gas cabinet to an atmosphere of freshly generated magnesium oxide plus approximately 10 per cent. carbon dioxide for from fifteen minutes to three hours. Two cats were used as controls to determine normal temperature variations. The experimental cats were confined in the chamber in individual wire cages, standing two deep, on stools 3 feet high. Control rectal temperatures on all cats were taken twice daily for several days before the experiment and just before fuming.

Magnesium Oxide Fume.—The magnesium oxide fume was generated by igniting 29 gm. of magnesium ribbon with a bunsen burner. To the magnesium oxide atmosphere was added carbon dioxide in approximately 10 per cent. concentration. Determinations of the density of the cloud and estimations of the concentrations of magnesium oxide breathed by the animals were made in the manner already described in our magnesium oxide experiments on man (7). Here again we have assumed the cat's respiratory volume, in the presence of 10 per cent. carbon dioxide, to be 4.1 liters per minute. Estimated magnesium oxide doses are given in Table 3 and are of the same order of magnitude as in the zinc oxide experiment.

Clinical Results.—The six experimental cats were exposed to magnesium oxide fume, one for 15 minutes; one for ½ hour; one for 1 hour; one for 2 hours; and two for 3 hours. The 15 minute, ½, 1, and 2 hour cats, when removed from the cabinet, were breathing somewhat rapidly. This soon subsided and there was no

TABLE 3.—ESTIMATED DOSAGE[1] OF CATS INHALING MAGNESIUM OXIDE FUME

CAT NO.	LENGTH OF EXPOSURE	ESTIMATED AMOUNT OF MAGNESIUM INHALED
	hr.	*mg.*
1	¼	21
2	½	39
3	1	70
4	2	126
5	3	156
6	3	156

[1] Dosage estimated on the basis of a 3-kg. animal.

TABLE 4.—TEMPERATURE FINDINGS IN CATS EXPOSED TO THE INHALATION OF MAGNESIUM OXIDE FUME PLUS 10 PER CENT. CARBON DIOXIDE

CAT NO.	LENGTH OF EXPOSURE	RECTAL TEMPERATURES PRECEDING AND DURING 20 HOURS FOLLOWING BEGINNING OF EXPOSURE		
		Immediately before Exposure	Following Exposure	
			Minimum	Maximum
	hr.	*°C.*	*°C.*	*°C.*
1	¼	39.0	38.1	39.4
2	½	38.9	38.3	39.1
3	1	38.5	38.1	39.1
4	2	39.6	38.0	39.7
5	3	39.5	37.5	39.8
6	3	38.8	35.3	38.7
20 control cats	normal range		37.8 to 39.8	

evidence of discomfort then or subsequently. The 3-hour cats were breathing in some distress when removed from the exposure chamber, felt decidedly cold to the touch, and seemed somewhat subdued. These animals, however, rapidly returned to normal and neither they nor the other cats showed subsequent ill effects. Cat 6, an animal exposed 3 hours and killed and autopsied 2 days after fuming, showed normal lungs. Owing to this finding and to the excellent health of the other animals, no further autopsies were done.

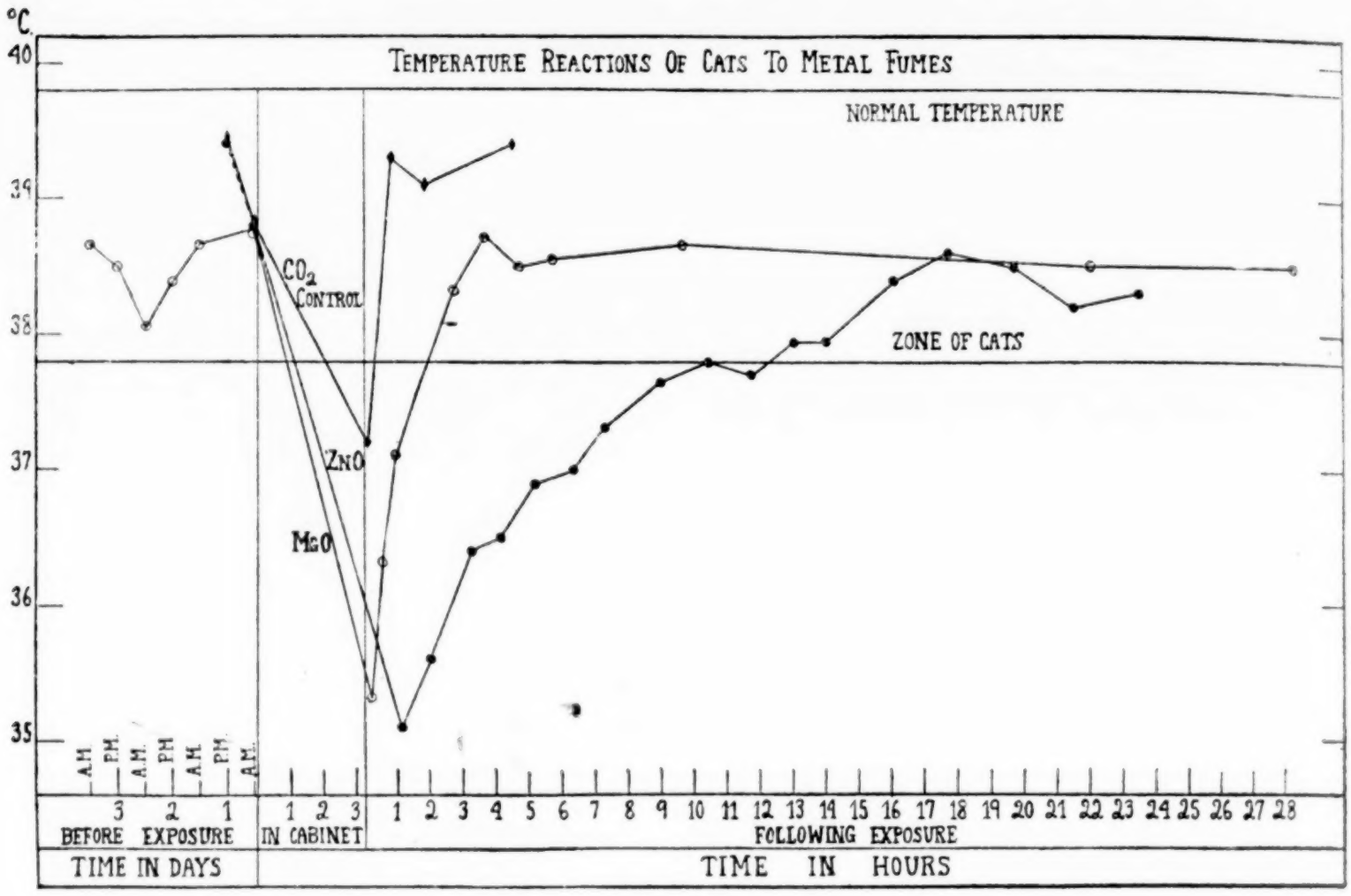

FIG. 3.—Rectal temperature reactions of three cats following prolonged single exposures (three hours to three hours and fifteen minutes) to atmospheres containing zinc oxide fume plus 10 per cent. carbon dioxide (Zinc Cat 10); magnesium oxide fume plus 10 per cent. carbon dioxide (Magnesium Cat 6); and air plus 10 per cent. carbon dioxide (Carbon Dioxide Cat 4).

Rectal temperatures, taken within five minutes of removal from the cabinet, then half-hourly, then hourly, and finally (after seven hours) at longer intervals, showed falls in temperature, milder in degree but similar in type to those occurring in cats exposed to zinc oxide. The significant temperature findings in the cats exposed to magnesium are given in Table 4. In Figure 3 are plotted the rectal temperature reactions of three cats exposed for from three hours to three hours and fifteen minutes, respectively, to atmospheres containing zinc oxide fume, magnesium oxide fume, and air, in each instance plus 10 per cent. carbon dioxide. The similarity of the two metal fume curves is obvious.

DISCUSSION

It was our purpose in performing the magnesium oxide experiment to determine whether a freshly formed metal

fume product (not a compound of a heavy metal) ordinarily considered insoluble and physiologically inert would, if inhaled in sufficient quantity, produce a reaction in animals analogous to that caused by the inhalation of zinc oxide fume. With these experiments as a preliminary, Drinker, Thomson, and Finn (7) have since shown that the inhalation of magnesium oxide produces in man a febrile reaction and a leukocytosis analogous to that caused by zinc oxide. These latter experiments on man, confirming as they do the analogous effects of inhaled, freshly generated zinc and magnesium oxide fumes, tend to confirm the validity of our animal experiments and to support our conclusion that a fall in temperature—of marked character and of prolonged duration in severely exposed cats and rats—may be regarded as a characteristic reaction of animals to the inhalation of freshly generated metal fume products. The findings of Turner and Thompson on guinea-pigs should be remembered in this connection. Although the magnesium in our experiments caused less marked results than did the zinc, it is our opinion that larger doses would, in all probability, produce severer reactions.

Summary and Conclusions

Rabbits, rats, and cats exposed in a gas chamber to the inhalation of freshly generated zinc oxide fume plus 10 per cent. carbon dioxide have shown uniformly falls in body temperature, slight and fairly transient following brief exposures, but of marked character and prolonged duration in animals (cats and rats) inhaling the fume for an hour or more. No significant abnormal rises in temperature occurred subsequently.

A reaction, similar in type but of milder degree, occurred in cats exposed to the inhalation, in approximately similar amounts, of freshly generated magnesium oxide fume plus 10 per cent. carbon dioxide. These experiments suggest that the characteristic reaction of animals to the inhalation of freshly formed metal fume products—analogous to the characteristic febrile reaction occurring in man—is a fall rather than a rise in temperature, the degree and duration depending on the species of animal, and on the severity and the duration of the exposure.

Our pathologic studies indicate that exposure to zinc oxide fume causes a heavy outpouring of polymorphonuclear leukocytes—a reaction to which there is a definite latency. In severely exposed animals, especially cats, the irritative process may go on to bronchopneumonia.

Zinc analyses on the lungs of exposed animals show that cats will inhale proportionately more zinc than will rats; that the amounts of zinc inhaled do not vary directly with the length of exposure but are proportionately much greater during the first fifteen to forty-five minutes; and that inhaled zinc oxide, even in large amounts, is rapidly removed from the lungs of animals, four days sufficing in both our severely exposed cats and rats for complete removal of the abnormal zinc.

As zinc is removed from the lungs of exposed animals and its concentra-

tion there diminishes, the zinc concentrations of the liver, gallbladder and bile, and kidney rise—these organs, together with the gastro-intestinal tract, being involved in the excretion of zinc. Simultaneously, the zinc concentration of the pancreas also rises, as it does with zinc fed animals. A possible excretory function of the pancreas is suggested in this connection.

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BOOKS RECEIVED

Books received are acknowledged in this column, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers and as space permits.

PERSONAL HYGIENE FOR WOMEN. By *Clelia Duel Mosher*, M.A., M.D., Associate Professor of Personal Hygiene and Medical Adviser of Women, Stanford University. Cloth. Pp. ix, 97 with index. California: Stanford University Press, 1927.

POTASSIUM AND TARTRATES. A REVIEW OF THE LITERATURE ON THEIR PHYSIOLOGICAL EFFECTS. By *Ralph W. Webster*, Ph.D., M.D., Professor of Medical Jurisprudence in University of Chicago (Rush Medical College), Chicago, Illinois; Director of Chicago Laboratory. With a Digest and Bibliography of the Literature by *W. A. Brennan*, A.B. Cloth. Pp. 168 with contents and index. Chicago: The Commonwealth Press, 1927.

INFECTIOUS DISEASES AND ASEPTIC NURSING TECHNIQUE. A HAND-BOOK FOR NURSES. By *Dennett L. Richardson*, M.D., Superintendent of the Providence City Hospital, Providence, R. I. Cloth. Pp. 182 with illustrations and index. Philadelphia and London: W. B. Saunders Co., 1927.

BOOK REVIEWS

GASES, DUST AND HEAT IN MINES. By *K. Neville Moss*. Pp. 233, illustrated. London: Chas. Griffin & Co., Ltd., 1927.

The book is an excellent example of applied physiology, and applied by a professor of engineering. Professor Moss deals with his subject from both the safety and the health sides showing how such mine gases as methane have characteristics which may render them explosively dangerous while physiologically inert, while others such as carbon monoxide are chiefly important on account of their poisonous nature.

Ventilation is required in coal mines primarily to wash out explosive mixtures and render the workings safe. But as mines go deeper and deeper they get hotter and the heat is often associated with humidity; hence wet bulb temperatures reaching 90°F. may occur which establish risk of heat stroke for those at work. Ventilation is needed to modify such conditions and the means to this end are as yet hardly understood.

The author throughout acknowledges his indebtedness to Dr. J. S. Haldane with whom he is closely associated and sets out clearly the physiologic problems involved. Similarly he deals with coal dust, innocuous to inhale but an explosive danger when mixed with air, and with rock dust, injurious to inhale particularly if composed of silica but useful for damping or preventing explosions.

The book is a good one and brings together much information recently acquired but difficult to find in articles distributed in diverse scientific journals.—*E. L. Collis.*

A SHORT MANUAL OF INDUSTRIAL HYGIENE. By *L. P. Lockhart*. Pp. 114. London: John Murray, 1927.

This little volume is good. It is written by one who is practising what

he preaches. It is intended for laymen who are in control of workers, and breathes the modern atmosphere of philanthropy surely based on economics. Simple but useful words tell of the hygiene of the person and of the place, of how to avoid common ailments and to keep clear of accidents, of first aid for injuries and for sickness. One chapter is wisely devoted to the young employee. Several good illustrations are used to demonstrate correct and incorrect lighting, and restful and faulty sitting postures. Dr. Lockhart has achieved success in explaining difficult matters in plain words.—*E. L. Collis.*

VENTILATION OF MINES. By *Walter S. Weeks*, A.B., S.B., M.E. (Harvard), Associate Professor of Mining, University of California. First Edition. Cloth. Pp. x, 228 with index; illustrated. New York and London: McGraw-Hill Book Co., Inc., 1926.

Professor Weeks' book fills a distinct gap in the literature of mining engineering and comes at an opportune time, in view of the present renewal of interest in mine ventilation. While the style of treatment is primarily that of a textbook, the data given, supplemented by the numerous references, are valuable to the practical mine ventilation engineer as well as to the student. The data relate more specifically to metal mines than to coal mines and lay particular stress on the physical and physiologic aspects.

The separate chapters relate to: physical properties of air; air measurements; flow of air in ducts; natural ventilation; mechanical ventilation; physiologic considerations; the ventilation system; and auxiliary ventilation. Many new data, not hitherto available except as scattered in the literature, are included in this book. The data contributed by the author's own researches and analyses are given a prominent place and are set forth in some detail. Many features of practical ventilation receive but slight attention and it is apparent that, in order to do justice to all phases of the subject, a much larger book will be required.—*G. E. McElroy.*

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